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### Title

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### Permalink

<https://escholarship.org/uc/item/1nh842bq>

### Journal

Open Urology and Nephrology Journal, 9(1)

### ISSN

1874-303X

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### Publication Date

2016-04-01

### DOI

10.2174/1874303X01609010044

Peer reviewed

# **Monocyte Chemotactic Protein-1 (MCP-1) as a Predictor of Imperfect or Prolonged Incontinence after Prostatectomy.**

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## Introduction

Prostate cancer is the most common non-cutaneous malignancy in men and is the 2<sup>nd</sup> leading cause of death from cancer in men.<sup>1</sup> Radical prostatectomy is one of the treatment options available for organ-confined disease.

Postoperative incontinence is a common side effect after prostatectomy that can severely impact quality of life.<sup>2-4</sup> The pathophysiology of incontinence is debated but most commonly thought to be due to sphincter insufficiency.<sup>5</sup>

However, a recent review of the literature has shown other factors leading to bladder dysfunction after prostatectomy include detrusor overactivity, reduced bladder capacity, and impaired detrusor contractility.<sup>6</sup> Moreover, after prostatectomy patients may develop de novo overactive bladder (OAB) symptoms, which may or may not be detectable on urodynamic evaluation as detrusor overactivity (DO).<sup>7</sup> Currently, there are no preoperative factors that may allude to postoperative incontinence.

Using a proteomics chip based analysis of urinary cytokine expression, Monocyte Chemotactic Protein-1 (MCP-1) was found to have two-fold higher expression over the other groups making it a potential target for an OAB biomarker compared to UTI and controls.<sup>8</sup> Herein, we prospectively investigate OAB and inflammation using urinary MCP-1 associated with the outcome of 30-day urinary continence after robotic radical prostatectomy (RRP).



## **Materials and Methods**

### **Patient Population**

After institutional review board approval, we enrolled men with biopsy proven prostate cancer undergoing pre-operative evaluation for robotic assisted radical prostatectomy. One hundred twenty men underwent informed consent and provided a urine sample. The patient's serum laboratory studies, urine analysis, uroflowmetry results, and post-void residual were recorded. The patient also completed the Sexual Health Inventory for Men (SHIM) and the International Prostate Symptom Score (IPSS) questionnaires, including the urinary quality of life (QOL) question. In order to minimize differences in surgical technique, we only enrolled patients in which the robotic radical prostatectomy was performed by a single surgeon (TA). The nerve sparing technique was decided by the primary surgeon in a case-by-case base and documented. Patients were excluded from final analysis if they had previous radiation therapy (n=2), pT4 disease (n=1), chronic inflammation on final pathology (n=11), active urinary tract infection, or taking anticholinergic medication perioperatively (n=25). Non-white ethnicity was excluded due to very limited numbers (n=4).

### **Urine Sample Collection and Processing**

The urine samples are collected when the bladder was 'extremely full' and participants had a strong desire to void. The patient voided and the urofloimetry characteristics were collected such as the volume of void (VV),

peak flow rate (PFR), and post void residual (PVR). The total volume in the bladder was calculated by adding VV to PVR. The urine was placed on ice immediately and transferred to the laboratory for preparation for storage. The urine samples were centrifuged at 3000g for 10 min at 4°C. The supernatant was separated into aliquots in 1.5 mL tubes and preserved in a freezer at -80°C.

#### Monocyte Chemotactic Protein - 1

The Quantikine Human MCP-1 Immunoassay (R&D Systems, Minneapolis, MN) is a 3.5-4.5 hour solid phase ELISA designed to measure MCP-1 in cell culture supernates, serum, plasma, and urine. All reagents were prepared as specified by the manufacturer including well washing then using 200 µL of substrate into each well, this was incubated for 30 minutes at room temperature. A stop solution was added to the wells then optical density of each well was performed using a microplate reader set to 450 nm. All measurements were performed in duplicate and the average used to subtract from the zero standard optical density. Initial evaluation from the manufacture had performed MCP-1 on 37 healthy volunteers and found an average of 211 pg/mL (range 42-410), however no further information regarding age, gender, or urinary symptoms are provided.

#### Follow-Up

We asked participants to return pre-postage stamped cards when they achieved continence landmarks including pad free status date. Patients kept continence logs for the first week after the catheter was removed. Patients that did not reach continent status or did not return logs were contacted by phone for updates. At the end of the study period (3 months post-operatively) patients with missing data were contacted via telephone.

### Statistical Analysis

Our primary outcome was 30-day continence defined as the use of zero pads at 30 days. The primary predictor variable was Monocyte chemotactic protein 1. Associations between MCP-1 and other variables were explored with the Spearman correlation coefficient or Mann-Whitney test. As secondary outcomes, we also investigate 7 day (early continence) and 60 day (delayed continence) associated with MCP-1. Continence is evaluated using the Chi-squared test at 7-day, 30-day, and 60-day time points. The univariate analysis was done with Chi-Squared tests and the multivariate analyses were performed with logistic regression.

## **Results**

After exclusions described in the methods 76 patients were included in analyses. Demographics of the group are in table 1. The distributions of both MCP-1 and MCP-1 adjusted for total bladder volume (MCP-1/TV) were not normal and skewed to the right. Therefore, a non-parametric Mann-Whitney test was used to test the difference in MCP-1 between those who were and

were not continent at 30 days. Men who were continent at 30 days did not differ significantly from those who were not continent with respect to MCP-1 ( $p=0.258$ ) or MCP after adjusting for bladder volume (MCP1/TV;  $p=0.14$ ). However, quartile results suggested that high MCP-1 and MCP-1/TV values were associated with a higher likelihood of incontinence at 30 days. Of men incontinent 30 days, 41% (14/34) were in the highest quartile of MCP1/TV compared to only 12% (5/42) of continent men (Chi-Squared,  $p=0.003$ ).

Correlations between MCP1 and other variables were investigated. The urinary creatinine ( $r=0.21$ ;  $p<0.001$ ) and the total bladder volume ( $r=-0.56$ ;  $p<0.001$ ) had the highest correlation. Other variables significantly correlated with MCP-1 include the sexual health inventory for men (SHIM;  $r=-0.24$ ;  $p=0.037$ ) and the American Urological Association symptom score (AUAss;  $r=0.25$ ,  $p=0.030$ ). No significant correlations were identified between MCP-1 and other demographic variables.

Men in the highest MCP-1/TV quartile were noted to have significantly higher incontinence at 7 days (10.5% vs. 35.1%;  $p=0.041$ ) and at 30 days (26.3 vs. 64.9%;  $p=0.003$ ) compared to all other quartiles combined. (Figure 1) At 60 days, the difference in continence rates for highest quartile of MCP1/TV vs. lower quartiles (68.4% vs. 78.9%;  $p=0.350$ ) was no longer statistically significant.



In univariant analysis only SHIM score ( $p=0.008$ ) and the highest quartile MCP1/TV ( $p=0.003$ ) were associated with 30-day continence. A logistic regression model was performed including MPC1/TV (highest quartile vs. lower quartiles), and SHIM as independent variables in the model. In addition, urinary creatinine was included in the model to account for urine concentration and bilateral nerve sparing was included as it trended to significance in univariant analysis. We noted that those in the highest quartile have a 78% chance of being incontinence at 30 days from robotic prostatectomy controlling for other factors (OR 0.22; 95% CI 0.058-0.80;  $p=0.022$ ).

## **Discussion**

High level of Monocyte chemotactic protein-1 corrected for total bladder volume is a predictor of 30-day continence after prostatectomy. Men in the highest quartile (MCP-1/TV  $>0.53$ ) are at a significant risk of delayed continence exceeding 30-days. These findings suggest that a preconditioned state of high inflammation may be present in some patients causing bladder pathology contributing to incontinence. The sentinel study leading to our investigation noted elevated expression of MCP-1 in patients with overactive bladder, which could account for incontinence due to the reduced urethral resistance from surgery.<sup>8</sup>

Men treated for bladder outlet obstruction treated by transurethral resection of the prostate (TURP) may have significant improvement in lower urinary tract symptoms after surgery; however 30-50% of men continue to have symptoms after surgery.<sup>9, 10</sup> In some men the reduced urethral resistance as seen after radical prostatectomy may unmask overactive bladder symptoms. Additionally, studies have shown OAB symptoms can occur de novo after radical prostatectomy.<sup>3, 5, 6</sup> Therefore, treating the OAB symptoms may improve or reduce the longevity of post-operative incontinence caused by unmasking OAB or de novo OAB.

Treating overactive bladder is typically performed with oral medications initially after physical exam to exclude strictures or other pathology. In a recent retrospective study on 94 patients, Duloxetine (a combined serotonin/norepinephrine reuptake inhibitor) has been shown to decrease post prostatectomy incontinence by 50% at 30 days though only 35% were able to tolerate the medications side effects.<sup>11</sup> A small-randomized (n=27) study with Tolterodine starting the day of surgery noted a significant reduction in early incontinence at 15 days (8% vs. 38%<sup>p</sup>=0.04) in men with preoperative moderate/severe lower urinary tract symptoms due to prostate enlargement.<sup>12</sup> These results suggest that medical treatment of OAB, in addition to pelvic floor exercises, may lessen the burden of early incontinence and potentially lead to faster recover of continence. MCP-1/TV may be a biomarker to identify subjects that may benefit more from OAB

therapy prior to prostatectomy in order to start medications early in the recovery process. Studies are limited regarding anti-inflammatory therapy to prevent post-operative incontinence. One recently evolving concept regarding reducing inflammation at the time of surgery is hypothermia of the prostate via a rectal balloon at the time of surgery.<sup>13</sup> All patients in this study receive hypothermia during prostatectomy, which has been shown to have a significant reduction in post prostatectomy incontinence.<sup>14</sup>

Currently, surgeons assess the patient's bladder symptoms using demographics and questionnaires prior to prostatectomy. A recent systematic review and meta-analysis of post-prostatectomy incontinence reported associations with age, BMI >30, comorbidities, severity of lower urinary tract symptoms, and preoperative erectile function.<sup>15</sup> We investigated these variables in our cohort and only noted preoperative sexual function (SHIM) to be a significant determinant of incontinence. One of the most significant factors for incontinence is the age of the patient; however, our study enrolled many men of similar age group likely causing age to have a negligible effect in this study population.<sup>16</sup> A previous study noted urinary leakage at 4-7 days after surgery was predictive of long-term post-prostatectomy incontinence; however, this is a post-operative tool and would not be useful in preoperative patient counseling. We propose a larger study potentially in the context of a clinical trial to confirm the results of MCP-1 as a urinary biomarker to predict post-operative continence. The

information obtained from such a biomarker could weigh heavily in the discussion regarding radical prostatectomy expectations and an individualized treatment plan, which may include pre-operative pelvic therapy and early use of medications.

Limitations of the study are the small sample size and homogeneous nature of our population especially with regard to age and race/ethnicity. We specifically chose to use strict entry criteria for this pilot study to show proof of concept and obtain preliminary data to justify inclusion into a clinical trial. We feel the prospective nature of the study and the addition of bladder volume in addition to urinary concentration studies are novel in post-prostatectomy incontinence.

## **Conclusions**

Monocyte chemotactic protein – 1 is a novel urinary biomarker that may have the ability to predict 30-day post-prostatectomy incontinence. The ability to predict urinary incontinence could provide clinicians and patient's valuable information for shared-decision making and potentially an individualized recovery plan with appropriate expectations. Further studies with larger and broader populations are needed for confirmation of these findings.

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## **Tables/Figures**

Table 1: Demographics of 30-Day Continence Populations

Table 2: Univariate and Multivariate analysis achieving 30 day continence.

Figure 1: Bar graph representing zero pad continence at selected time points for the highest quartile MCP-1/TV